Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

Downloaded from https://aidsinfo.nih.gov/guidelines on 8/31/2020

Zidovudine (ZDV, Retrovir) (Last updated April 14, 2020; last reviewed April 14, 2020)

Formulations

Capsule: 100 mg
Syrup: 10 mg/mL
Concentrate for Injection or Intravenous Infusion: 10 mg/mL (Retrovir)

Generic Formulations:

- 100 mg capsule
- 10 mg/mL syrup
- 300 mg tablet

Fixed-Dose Combination Tablets:

- [Combivir and generic] Lamivudine 150 mg/zidovudine 300 mg (scored)
- [Trizivir and generic] Abacavir 300 mg/lamivudine 150 mg/zidovudine 300 mg

When using fixed-dose combination (FDC) tablets, refer to other sections of the Drug Appendix for information about the individual components of the FDC. See also Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents.

For additional information, see Drugs@FDA or DailyMed.

Dosing Recommendations

Note: Zidovudine (ZDV) is frequently used in neonates to prevent perinatal transmission of HIV. See Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection and Table 12 for information about using ZDV to prevent perinatal transmission.

Recommended Neonatal Dose for Treatment of HIV by Gestational Age at Birth[a]

Gestational Age at Birth	Oral ZDV Dose
≥35 weeks	**Birth to Age 4 Weeks:** • ZDV 4 mg/kg twice daily; *or* • Alternative simplified weight-band dosing **Simplified Weight-Band Dosing for Infants with a Gestational Age ≥35 Weeks at Birth:** **Note:** The doses in this table provide approximately ZDV 4 mg/kg twice daily from birth to age 4 weeks. **Aged >4 Weeks:** • ZDV 12 mg/kg twice daily

Weight Band	Twice-Daily Volume of ZDV 10 mg/mL Syrup
2 kg to <3 kg	1 mL
3 kg to <4 kg	1.5 mL
4 kg to <5 kg	2 mL

Selected Adverse Events

- Bone marrow suppression leading to anemia and neutropenia; macrocytosis with or without anemia.
- Nausea, vomiting, headache, insomnia, asthenia
- Lactic acidosis/severe hepatomegaly with hepatic steatosis
- Lipodystrophy and lipoatrophy
- Myopathy (associated with prolonged use of ZDV) and myositis

Special Instructions

- Give ZDV without regard to food.
- If substantial granulocytopenia or anemia develops in patients who are receiving ZDV, it may be necessary to discontinue therapy until bone marrow recovery is observed. In this setting, some patients may require erythropoietin or filgrastim injections or transfusions of red blood cells.
- Screen patients for hepatitis B virus (HBV) infection before using FDC products that contain lamivudine (3TC). Severe acute exacerbation of HBV infection can occur when 3TC is discontinued; therefore, hepatic

Gestational Age at Birth	Oral ZDV Dose
≥30 weeks to <35 weeks	**Birth to Age 2 Weeks:** • ZDV 2 mg/kg twice daily **Aged 2 Weeks to 6 to 8 Weeks:** • ZDV 3 mg/kg twice daily **Aged >6 Weeks to 8 Weeks:** • ZDV 12 mg/kg twice daily
<30 weeks	**Birth to Age 4 Weeks:** • ZDV 2 mg/kg twice daily **Aged 4 Weeks to 8 to 10 Weeks:** • ZDV 3 mg/kg twice daily **Aged >8 Weeks to 10 Weeks:** • ZDV 12 mg/kg twice daily

Note: For infants who are unable to tolerate oral agents, the intravenous dose should be 75% of the oral dose, but the dosing interval should remain the same.

Infant (Aged ≥35 Weeks Post-Conception and ≥4 Weeks Post-Delivery, Weighing ≥4 kg) and Child Dose

Weight-Based Dosing for Zidovudine

Weight	Twice-Daily Dosing
4 kg to <9 kg	12 mg/kg
9 kg to <30 kg	9 mg/kg
≥30 kg	300 mg

Alternative Body Surface Area Dosing

Oral:

- ZDV 180 mg to 240 mg per m^2 of body surface area every 12 hours

Child and Adolescent (Weighing ≥30 kg) and Adult Dose:

- ZDV 300 mg twice daily

[Combivir and Generic] Lamivudine/Zidovudine

Child and Adolescent (Weighing ≥30 kg) and Adult Dose:

- One tablet twice daily

[Trizivir and Generic] Abacavir/Lamivudine/Zidovudine

Child and Adolescent (Weighing ≥30 kg) and Adult Dose:

- One tablet twice daily

function should be monitored for several months after patients with HBV infection stop taking 3TC.

Metabolism/Elimination

- ZDV is eliminated primarily by hepatic metabolism. The major metabolite is ZDV glucuronide, which is renally excreted.
- ZDV is phosphorylated intracellularly to active ZDV-triphosphate.

Zidovudine Dosing in Patients with Renal Impairment:

- A dose adjustment is required for ZDV in patients with renal insufficiency.

Zidovudine Dosing in Patients with Hepatic Impairment:

- The dose of ZDV may need to be reduced in patients with hepatic impairment.
- Do not use FDC products (e.g., Combivir, Trizivir) in patients with creatinine clearance <50 mL/min, patients who are on dialysis, or patients who have impaired hepatic function.

[a] For premature infants who receive an HIV diagnosis, the time to change to the continuation dose varies with post-gestational age and clinical status of the infant.

Drug Interactions (see also the Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker)

- *Bone marrow suppressive/cytotoxic agents, including ganciclovir, valganciclovir, interferon alfa, and ribavirin:* These agents may increase the hematologic toxicity of zidovudine (ZDV).
- *Nucleoside analogues that affect DNA replication:* Nucleoside analogues, such as ribavirin, antagonize *in vitro* antiviral activity of ZDV.
- *Doxorubicin:* Simultaneous use of doxorubicin and ZDV **should be avoided**. Doxorubicin may inhibit the phosphorylation of ZDV to its active form.

Major Toxicities

- *More common:* Hematologic toxicity, including neutropenia and anemia, particularly in patients with advanced HIV disease. Headache, malaise, nausea, vomiting, and anorexia. Neutropenia may occur more frequently in infants who are receiving both lamivudine (3TC) and ZDV than in infants who are receiving only ZDV.[1]
- *Less common (more severe):* Myopathy (associated with prolonged use), myositis, and liver toxicity. Cases of lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Fat maldistribution.
- *Rare:* There is a possible increased risk of cardiomyopathy.[2,3]

Resistance

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation.

Pediatric Use

Approval

ZDV is frequently included as a component of the nucleoside reverse transcriptase inhibitor (NRTI) backbone for antiretroviral therapy (ART), and it has been studied in children in combination with other NRTIs, including abacavir (ABC) and 3TC.[4-20] Pediatric experience with ZDV both for treating HIV and for preventing perinatal transmission is extensive. However, the mitochondrial toxicity of ZDV leads many experts to favor the use of ABC or tenofovir alafenamide in cases where the patient's age and the results of viral resistance testing do not restrict the use of these drugs.

Efficacy in Clinical Trials

The combination of ZDV and 3TC has been extensively studied in children and has been a part of antiretroviral (ARV) regimens in many trials. The safety and efficacy of ZDV plus 3TC were compared to the safety and efficacy of ABC plus 3TC and stavudine (d4T) plus 3TC in children aged <5 years in the CHAPAS-3 study. All regimens also included either nevirapine or efavirenz. All the NRTIs had low toxicity and produced good clinical, immunologic, and virologic responses.[21] Pediatric patients who received ZDV plus ABC or ZDV plus 3TC had lower rates of viral suppression and experienced more adverse events that required regimen modification than patients who received ABC plus 3TC.[22,23]

Infants with Perinatal HIV Exposure

The PACTG 076 clinical trial demonstrated that administering ZDV to pregnant women and their infants could reduce the risk of perinatal HIV transmission by nearly 70%.[24] See Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection for further discussion on using ZDV to prevent perinatal transmission of HIV. A dose of approximately ZDV 4 mg/kg of body weight every 12 hours is recommended for prevention of perinatal HIV transmission in neonates and infants with gestational ages ≥35 weeks. Infants who have been exposed to HIV but who are uninfected should continue on the prophylactic dose for 4 to 6 weeks, depending on their gestational age at time of delivery and the risk assessment for perinatal transmission.

Simplified, alternative weight-band dosing has also been developed, and the rationale for these doses is based on the intracellular metabolism of ZDV (see Pharmacokinetics below). The rate-limiting step in the phosphorylation of ZDV to active ZDV triphosphate is the limited amount of thymidylate kinase. Increasing the dose of ZDV will lead to increased ZDV plasma concentrations and increased intracellular concentrations of ZDV monophosphate, but not ZDV diphosphate or ZDV triphosphate.

In 31 infants who received ZDV to prevent perinatal transmission, levels of intracellular ZDV metabolites were measured after delivery. Plasma ZDV and intracellular ZDV monophosphate decreased by roughly 50% between post-delivery Day 1 and Day 28, whereas ZDV diphosphate and ZDV triphosphate remained low throughout the sampling period.[25] ZDV dose is poorly correlated with the active form of ZDV that is found intracellularly. Because of this, a simplified weight-band dosing approach can be used for the first 4 weeks of life in infants with gestational ages ≥35 weeks (see the dosing table above). This approach should simplify the minor dose adjustments that are commonly made based on changes in infant weight during ZDC use in the first 4 weeks of life and will make it easier for caregivers to administer ZDV oral syrup to their infants. The changes in weight and the small differences in ZDV dose will have minor effects on the intracellular concentrations of ZDV triphosphate.

Infants with HIV Infection

For full-term neonates who receive an HIV diagnosis during the first days to weeks of life, the ZDV dose should be increased to the continuation dose at age 4 weeks (see the dosing table above). The activity of the enzymes responsible for glucuronidation is low at birth and increases dramatically during the first 4 to 6 weeks of life in full-term neonates. This increase in metabolizing enzyme activity leads to an increased clearance of plasma ZDV, and the dose of ZDV should be adjusted when ZDV is used to treat HIV after the first 4 weeks in full-term infants.

For premature infants who receive an HIV diagnosis, the time to increase the ZDV dose from the initial dose varies with post-gestational age and the clinical status of the neonate. On the basis of population pharmacokinetic (PK) modeling and simulations and data from studies that have evaluated ZDV PKs in premature infants, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV recommends the following:

- For infants with HIV born at ≥30 weeks to <35 weeks, switch to a dose of ZDV 12 mg/kg twice daily at a post-gestational age of 6 to 8 weeks.
- For infants born at <30 weeks, switch to ZDV 12 mg/kg twice daily at a post-gestational age of 8 to 10 weeks.[26]

Clinicians should perform a careful clinical assessment of the infant, evaluate hepatic and renal function, and review concomitant medications before increasing the ZDV dose to the dose recommended for full-term infants.

Pharmacokinetics

ZDV undergoes intracellular metabolism to achieve its active form, ZDV triphosphate. Phosphorylation requires multiple steps: ZDV is phosphorylated by thymidine kinase to ZDV monophosphate; ZDV monophosphate is phosphorylated by thymidylate kinase to ZDV diphosphate; and ZDV diphosphate is phosphorylated by nucleoside diphosphate kinase to ZDV triphosphate. Overall, ZDV PKs in pediatric patients aged >3 months are similar to those seen in adults. Although the mean half-life of intracellular ZDV triphosphate (9.1 hours) is considerably longer than that of unmetabolized ZDV in plasma (1.5 hours), once-daily ZDV dosing is not recommended because of the low intracellular ZDV triphosphate concentrations seen with 600-mg, once-daily dosing in adolescents.[27] PK studies such as PACTG 331 demonstrate that dose adjustments are necessary for premature infants, because they have reduced clearance of ZDV compared with the clearance observed in term newborns of similar postnatal ages.[5] ZDV has good central nervous system (CNS) penetration (cerebrospinal fluid-to-plasma concentration ratio is 0.68), and ZDV has been used in children with HIV-related CNS disease.[16]

Toxicity

Several studies suggest that the adverse hematologic effects of ZDV may be concentration-dependent, with a higher risk of anemia and neutropenia in patients with higher mean plasma area under the curve values for ZDV.[4,5,28] A significant reduction in the incidence of hematologic toxicity was observed during a retrospective analysis of infants who received a short course of ZDV (2 weeks) to prevent perinatal HIV transmission.[29] In this study, 137 infants received ZDV for 2 weeks, and 184 infants received ZDV for >2 weeks; of these infants, 168 (91.3%) received 4 weeks of ZDV prophylaxis. The risk of anemia (defined as a Division of AIDS [DAIDS] severity grade of mild or higher) was significantly lower in the short-course group at both age 1 month ($P < 0.001$) and age 3 months ($P < 0.001$).[29] Some national guidelines, including those from Germany/Austria and Great Britain, recommend a minimum of 2 weeks of post-exposure prophylaxis in infants at low risk or very low risk of HIV transmission.[29,30] Current U.S. guidelines recommend 4 weeks of prophylaxis for infants at low risk of HIV transmission. For infants who develop significant anemia while receiving ZDV for prevention of perinatal HIV transmission, early discontinuation may be considered for infants who are determined to be at a low risk of transmission after expert consultation.

Incidence of hematological toxicity was investigated in the ARROW study, which randomized ART-naive Ugandan and Zimbabwean children to receive either ZDV-containing regimens or ABC-containing regimens. The incidence of severe anemia was similar regardless of ZDV use, and this finding suggests that advanced HIV disease contributed to low hemoglobin values. ZDV use was associated with severe neutropenia in a small number of children.[31]

ZDV is associated with greater mitochondrial toxicity than ABC and tenofovir disoproxil fumarate, but it is associated with less mitochondrial toxicity than d4T.[32,33]

While the incidence of cardiomyopathy associated with perinatal HIV infection has decreased dramatically since the use of ART became routine, the use of a regimen that contains ZDV may increase the risk.[2] Analysis of data from a U.S.-based, multicenter, prospective cohort study (PACTG 219/219C) found that ongoing ZDV exposure was independently associated with a higher rate of cardiomyopathy.[2] As part of the Pediatric HIV/AIDS Cohort Study (PHACS)/Adolescent Master Protocol (AMP) study, echocardiogram measurements were collected between 2008 and 2010 in 325 youth aged 7 to 16 years with perinatally acquired HIV infection. An association between ZDV use and increased end-systolic wall stress was observed in this study. The investigators speculate that alterations in cardiac structure in these children could progress to symptomatic cardiomyopathy later in life.[3]

References

1. Nielsen-Saines K, Watts DH, Veloso VG, et al. Three postpartum antiretroviral regimens to prevent intrapartum HIV infection. *N Engl J Med*. 2012;366(25):2368-2379. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22716975.

2. Patel K, Van Dyke RB, Mittleman MA, et al. The impact of HAART on cardiomyopathy among children and adolescents perinatally infected with HIV-1. *AIDS.* 2012;26(16):2027-2037. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22781228.

3. Williams PL, Correia K, Karalius B, et al. Cardiac status of perinatally HIV-infected children: assessing combination antiretroviral regimens in observational studies. *AIDS.* 2018;32(16):2337-2346. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30102660.

4. Balis FM, Pizzo PA, Murphy RF, et al. The pharmacokinetics of zidovudine administered by continuous infusion in children. *Ann Intern Med.* 1989;110(4):279-285. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2643914.

5. Capparelli EV, Mirochnick M, Dankner WM, et al. Pharmacokinetics and tolerance of zidovudine in preterm infants. *J Pediatr*. 2003;142(1):47-52. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12520254.

6. Chadwick EG, Rodman JH, Britto P, et al. Ritonavir-based highly active antiretroviral therapy in human immunodeficiency virus type 1-infected infants younger than 24 months of age. *Pediatr Infect Dis J.* 2005;24(9):793-800. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16148846.

7. Englund JA, Baker CJ, Raskino C, et al. Zidovudine, didanosine, or both as the initial treatment for symptomatic HIV-infected children. AIDS Clinical Trials Group (ACTG) Study 152 Team. *N Engl J Med*. 1997;336(24):1704-1712. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9182213.

8. Jankelevich S, Mueller BU, Mackall CL, et al. Long-term virologic and immunologic responses in human immunodeficiency virus type 1-infected children treated with indinavir, zidovudine, and lamivudine. *J Infect Dis.* 2001;183(7):1116-1120. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11237839.

9. King JR, Kimberlin DW, Aldrovandi GM, Acosta EP. Antiretroviral pharmacokinetics in the paediatric population: a review. *Clinical Pharmacokinet.* 2002;41(14):1115-1133. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12405863.

10. Luzuriaga K, Bryson Y, Krogstad P, et al. Combination treatment with zidovudine, didanosine, and nevirapine in infants with human immunodeficiency virus type 1 infection. *N Engl J Med*. 1997;336(19):1343-1349. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9134874.

11. McKinney RE, Jr., Maha MA, Connor EM, et al. A multicenter trial of oral zidovudine in children with advanced human immunodeficiency virus disease. The Protocol 043 Study Group. *N Engl J Med*. 1991;324(15):1018-1025. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1672443.

12. McKinney RE, Jr., Johnson GM, Stanley K, et al. A randomized study of combined zidovudine-lamivudine versus didanosine monotherapy in children with symptomatic therapy-naive HIV-1 infection. The pediatric AIDS clinical trials group protocol 300 study team. *J Pediatr*. 1998;133(4):500-508. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9787687.

13. Mueller BU, Nelson RP, Jr., Sleasman J, et al. A Phase I/II study of the protease inhibitor ritonavir in children with human immunodeficiency virus infection. *Pediatrics*. 1998;101(3 Pt 1):335-343. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9480994.

14. Mueller BU, Sleasman J, Nelson RP, Jr., et al. A Phase I/II study of the protease inhibitor indinavir in children with HIV infection. *Pediatrics*. 1998;102(1 Pt 1):101-109. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9651421.

15. Palacios GC, Palafox VL, Alvarez-Munoz MT, et al. Response to two consecutive protease inhibitor combination therapy regimens in a cohort of HIV-1-infected children. *Scand J Infect Dis.* 2002;34(1):41-44. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11874163.

16. Pizzo PA, Eddy J, Falloon J, et al. Effect of continuous intravenous infusion of zidovudine (AZT) in children with symptomatic HIV infection. *N Engl J Med*. 1988;319(14):889-896. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3166511.

17. Saez-Llorens X, Nelson RP, Jr., Emmanuel P, et al. A randomized, double-blind study of triple nucleoside therapy of abacavir, lamivudine, and zidovudine versus lamivudine and zidovudine in previously treated human immunodeficiency virus type 1-infected children. The CNAA3006 Study Team. *Pediatrics*. 2001;107(1):E4. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11134468.

18. van Rossum AM, Geelen SP, Hartwig NG, et al. Results of 2 years of treatment with protease-inhibitor--containing antiretroviral therapy in dutch children infected with human immunodeficiency virus type 1. *Clin Infect Dis*. 2002;34(7):1008-1016. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11880968.

19. Bergshoeff AS, Fraaij PL, Verweij C, et al. Plasma levels of zidovudine twice daily compared with three times daily in six HIV-1-infected children. *J Antimicrob Chemother*. 2004;54(6):1152-1154. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15537694.

20. Nachman SA, Stanley K, Yogev R, et al. Nucleoside analogs plus ritonavir in stable antiretroviral therapy-experienced HIV-infected children: a randomized controlled trial. Pediatric AIDS Clinical Trials Group 338 Study Team. *JAMA*.

2000;283(4):492-498. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10659875.

21. Mulenga V, Musiime V, Kekitiinwa A, et al. Abacavir, zidovudine, or stavudine as paediatric tablets for African HIV-infected children (CHAPAS-3): an open-label, parallel-group, randomised controlled trial. *Lancet Infect Dis*. 2016;16(2):169-179. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26481928.

22. Green H, Gibb DM, Walker AS, et al. Lamivudine/abacavir maintains virological superiority over zidovudine/lamivudine and zidovudine/abacavir beyond 5 years in children. *AIDS.* 2007;21(8):947-955. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17457088.

23. Paediatric European Network for Treatment of AIDS (PENTA). Comparison of dual nucleoside-analogue reverse-transcriptase inhibitor regimens with and without nelfinavir in children with HIV-1 who have not previously been treated: the PENTA 5 randomised trial. *Lancet*. 2002;359(9308):733-740. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11888583.

24. Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. *N Engl J Med*. 1994;331(18):1173-1180. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7935654.

25. Kinai E, Kato S, Hosokawa S, et al. High plasma concentrations of zidovudine (AZT) do not parallel intracellular concentrations of AZT-triphosphates in infants during prevention of mother-to-child HIV-1 transmission. *J Acquir Immune Defic Syndr*. 2016;72(3):246-253. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26859826.

26. Capparelli EV, Englund JA, Connor JD, et al. Population pharmacokinetics and pharmacodynamics of zidovudine in HIV-infected infants and children. *J Clin Pharmacol*. 2003;43(2):133-140. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12616665.

27. Flynn PM, Rodman J, Lindsey JC, et al. Intracellular pharmacokinetics of once versus twice daily zidovudine and lamivudine in adolescents. *Antimicrob Agents Chemother.* 2007;51(10):3516-3522. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17664328.

28. Fillekes Q, Kendall L, Kitaka S, et al. Pharmacokinetics of zidovudine dosed twice daily according to world health organization weight bands in Ugandan HIV-infected children. *Pediatr Infect Dis J.* 2014;33(5):495-498. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24736440.

29. Nguyen TTT, Kobbe R, Schulze-Sturm U, et al. Reducing hematologic toxicity with short course postexposure prophylaxis with zidovudine for HIV-1 exposed infants with low transmission risk. *Pediatr Infect Dis J.* 2019;38(7):727-730. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31033907.

30. British HIV Association. BHIVA guidelines on the management of HIV in pregnancy and postpartum 2018 (2019 interim update). 2019. Available at: https://www.bhiva.org/pregnancy-guidelines.

31. Musiime V, Cook A, Nahirya Ntege P, et al. The effect of long-term zidovudine on hematological parameters in the ARROW randomized trial. Presented at: The Conference on Retroviruses and Opportunistic Infections. 2015. Seattle, Washington.

32. Moyle GJ, Sabin CA, Cartledge J, et al. A randomized comparative trial of tenofovir DF or abacavir as replacement for a thymidine analogue in persons with lipoatrophy. *AIDS.* 2006;20(16):2043-2050. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17053350.

33. Carr A, Workman C, Smith DE, et al. Abacavir substitution for nucleoside analogs in patients with HIV lipoatrophy: a randomized trial. *JAMA*. 2002;288(2):207-215. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12095385.